UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,580	11/21/2003	Bruce J. Dolnick	03551.0143	3209

26712 7590 08/14/2006

HODGSON RUSS LLP
ONE M & T PLAZA
SUITE 2000
BUFFALO, NY 14203-2391

EXAMINER	
PROUTY, REBECCA E	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/719,580	DOLNICK ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *15-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election without traverse of Group I, claims 1-14 in the reply filed on 5/30/06 is acknowledged.

Claims 15-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/30/06.

Claim 1 is objected to because of the following informalities: abbreviations (i.e., TBE) should not be used in the claims without first setting forth the full text for which they are used.

Claim 9 is objected to because of the following informalities: the word "one needs to be inserted after "least" in line 1. Appropriate correction is required.

Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 8, and 9 (upon which claims 3-7 and 10-14 depend) is indefinite in the recitation of "TBE1" and "TBE2". The specification on page 7 defines TBE1 as "any DNA or RNA that binds to TS in the manner similar to the naturally occurring TBE1 whereby translation of TS mRNA is interfered with and

wherein the naturally occurring TBE1 is the region of mRNA in the 5' noncoding region defined by the 36 nucleotide sequence in the human TS mRNA as described by Chu et. a1., (Proc. Natl. Acad. Sci. USA 90:517-521, 1993)" and defines the term "TBE2" as "any DNA or RNA that binds to TS in a manner similar to the naturally occurring TBE2 whereby translation of TS mRNA is interfered with and wherein the naturally occurring TBE2 is the region of mRNA defined by 70 nucleotide sequence in the human TS mRNA corresponding to nucleotides 480-550." However, these definitions themselves are indefinite as the specification does not make clear what is meant by "binds to TS in a manner similar to the naturally occurring TBE1 (or TBE2)" as it does not set forth any characteristics of the binding of the naturally occurring TBE1 (or TBE2) sequences which must be present in a variant sequence for it to be considered similar. Furthermore, as the only feature that clearly must be present is the ability to bind TS so as to inhibit translation of a downstream gene, it is unclear what characteristics differentiate TBE1 and TBE2 sequences as both SEQ ID NO:2 (i.e., a TBE1 sequence) and SEQ ID NO:3 (i.e., a TBE2 sequence) bind TS so as to inhibit translation of a downstream gene. As such the scope of sequence variants encompassed by these terms is entirely unclear.

Claims 1-4, 6, 8-11, and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of methods of identifying thymidylate synthase (TS) inhibitors using a reporter construct comprising a genus of TBE cassettes wherein a TBE cassette comprises a TBE1 sequence in either the forward or reverse direction and a TBE2 sequence in either the forward or reverse direction. The specification teaches the structure of only a single representative species of such TBE cassettes i.e., SEQ ID NO:1 which includes the TBE1 sequence of SEQ ID NO:2 and the TBE2 sequence of SEQ ID NO:3. Moreover, the specification fails to describe any other representative species of TBE cassettes by any identifying characteristics or properties other than the functionality of binding TS so as to inhibit translation of a downstream gene. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact

terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 1-4, 6, 8-11, and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of identifying TS inhibitors using a reporter construct comprising a TBE cassettes wherein the TBE cassette comprises SEQ ID NOS: 2 and 3, does not reasonably provide enablement for methods of identifying TS inhibitors using a reporter construct comprising any TBE cassette. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-4, 6, 8-11, and 13 are so broad as to encompass methods of identifying TS inhibitors using a reporter construct comprising any TBE cassette wherein a TBE cassette comprises a TBE1 sequence in either the forward or reverse direction and a TBE2 sequence in either the forward or reverse direction. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of TBE cassettes used in the methods of the claims. Since the nucleotide sequence of a protein binding element of a nucleic acid determines its structural and functional

properties, predictability of which changes can be tolerated in the nucleotide sequence and obtain the desired activity requires a knowledge of and guidance with regard to which nucleotides in the protein binding element's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein binding elements' structure relates to its function. Furthermore, Lin et al (Ref. 1 of applicants IDS) clearly teach that the natural TBE2 sequence is non-functional for inhibiting translation of a downstream gene in the reverse orientation (see specifically page 1386) clearly indicating that not only the sequence but the orientation of the sequence are important for its function. However, in this case the disclosure is limited to the TBE cassette of SEQ ID NO:1.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein binding element's sequence where nucleotide modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein binding element and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a

given protein binding element to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass methods of identifying TS inhibitors using a reporter construct comprising any TBE cassette because the specification does **not** establish: (A) regions of the TBE cassette structure which may be modified without effecting translation inhibitory activity; (B) the general tolerance of TBE cassettes to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any nucleotide residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including methods of identifying TS inhibitors using a reporter construct comprising any TBE cassette. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of TBE cassettes having the desired biological characteristics

for use in the claimed methods is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 7 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ novel vectors (i.e., pG3E1-2TBE and pG3E1-2TBE-Neo. Since the vectors are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The claimed plasmids' sequences are not fully disclosed, nor have all the sequences required for their construction been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. ə 112 may be satisfied by a deposit of the plasmids. The specification does not disclose a repeatable process to obtain the vectors and it is not apparent if the DNA sequences are readily available to the public. Accordingly, it is deemed that a deposit of these plasmids should have been made in accordance with 37 CFR 1.801-1.809.

If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be available to the public under the conditions specified in 37 CFR 1.808, would satisfy the deposit requirement made herein.

If the deposit is not made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

1. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request;
2. upon granting of the patent the strain will be available to the public under the conditions specified in 37 CFR 1.808;
3. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and
4. the deposit will be replaced if it should ever become inviable.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6, 8-11, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (Ref. 1 of applicants IDS) in view of Chu et al.

Lin et al teach methods of identifying a TS inhibitor comprising growing a culture of a cell transfected with a reporter construct in the presence and absence of a compound, lysing the cells, and assaying the lysates for reporter activity wherein the compound is a TS inhibitor if the reporter activity in the presence of the compound is increased compared to the reporter activity in the absence of the compound. (see particularly Figure 6) The reporter construct of Lin et al. comprises a ERG-1 promoter, a TS binding element from the human TS gene (i.e., nucleotides 480-550, nucleotides 480-580 or nucleotides 434-634) corresponding to TBE2 as described in the instant application and a luciferase reporter gene linked in a 5′ to 3′ direction such that the promoter and TBE element regulate the transcription and translation of the reporter gene.

As such the methods of Lin et al. differ from those claimed only in that the reporter constructs recited in the instant claims include both a TBE1 sequence and a TBE2 sequence while the constructs of Lin et al. includes only the TBE2 sequence.

Chu et al. teach that the translation of the human TS gene is autoregulated by the presence of two TS binding elements, one at nucleotides 75-110 of the human TS message and one within nucleotides 434-634. Each of these sequences bind to human TS and binding of the protein inhibits translation thereof.

Lin et al. teach on page 1385 that "the results from these experiments suggest that the 5′ upstream binding sequence is insufficient to allow complete translation repression by TS. It would appear then that the 5′ upstream sequence and the element in the protein coding region are both required for the process of TS translation autoregulation *in vitro*. Our preliminary findings suggest that these sequences function independently of one another." and on page 1388 that "*In vitro* translation experiments confirm that this specific RNA sequence (i.e. TBE2) is required along with the 5′ upstream element in order for human TS protein to exhibit its full range of translational autoregulatory activity.". In view of these teaching a skilled artisan would clearly be motivated to modify the reporter construct of Lin et al. which includes only the TBE2 sequence to

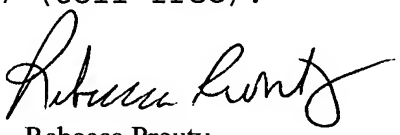
include the 5' upstream TS binding sequence also (i.e., nucleotides 75-110 of the human TS message as taught by Chu et al.) as Lin et al. clearly suggest that both sequences are necessary to provide a construct that would reproduce the regulatory features of the natural human TS gene. As Lin et al. clearly suggest that the two binding elements act independently and in order to prevent any steric interference of the two sites within such a reporter construct, it would have been obvious to a skilled artisan to separate the two binding elements from each other by a nucleotide linker sequence. Furthermore, as the ability to stably maintain such a reporter plasmid within the transfected cell would clearly enhance its usefulness for studying the regulation of the human TS gene as one would not need to repeat the transfection for every use, and as methods for integrating a plasmid into the genome of mammalian cells by including a selectable marker such the neo gene within the reporter plasmid and selecting for cells which have integrated the plasmid and can grow in the presence of the antibiotic G418 are well known in the art, it would have been obvious to include this gene in the construct and select for cells which stably maintain the construct.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner

can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Rebecca Prouty
Primary Examiner
Art Unit 1652